# Solid Mixtures of Homatropine and Cocaine as a Substitute for Atropine and Duboisine in Determining Refractive Errors.

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# SOLID MIXTURES OF HOMATROPINE AND COCAINE AS A SUBSTITUTE FOR ATROPINE AND DUBOISINE IN DETERMINING REFRACTIVE ERRORS.

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WITH the discomforts and drawbacks attendant upon the use of Atropine, employed for the determination of refractive errors, the profession is entirely familiar. The laity, too, are becoming more and more impatient of the ten days' to two weeks' partial blindness which often follows the instillation of Atropine Solutions when used for the purpose of prescribing glasses. Every oculist knows that many persons refuse to allow "drops" to be put into their eyes, mainly on account of the enforced absence from work which their use commonly entails. As long as Atropine is employed for the treatment of diseases that have already rendered the eyes unfit for work no complaint is raised, but the employment of a drug that dilates the pupil, blurs the sight for distant vision and makes near work out of the question, is extremely distasteful. More than that, there is a large percentage of the ametropic population urgently needing glasses who can not or will not spare the necessary time from business pursuits, and an almost equal number who cannot *be* spared, however willing they may themselves be to go through a "course" of Atropine. These individuals have to choose between submitting to an incomplete and perfunctory examination of the optician and jewelry-store order and allowing their refractive errors to go uncorrected.

I have devoted some months of the past year to experimenting with Mixtures of Homatropine (alkaloid, Merck) with Cocaine (alkaloid, Merck) and I hope to be able to show, in confirmation of Lang and Barrett's statements,[1] that when used in a certain definite manner and dose, and with proper excipients, this combination is a thoroughly reliable cycloplegic and quite as satisfactory as Atropine for determining the refractive state of ametropic eyes. Furthermore, the employment of this mixture is not followed by the annoying symptoms incident to the employment of Atropine, Duboisine, or Hyoscine. It accomplishes its purpose within an hour after being introduced into the conjunctival sac and the ciliary paralysis passes off, or may be made to pass off, within twelve or, at most, twenty-four hours.

Shortly after the discovery of Homatropine, by Ladenburg* of Kiel, some observers (Schell,[2] Pautynski,[3] *et al.*) experimented with it, and, as a result of

* Berichte über die Deutsch. Chem. Gesellschaft, Jan. 26, 1880.

these trials, entertained the belief that it would be found to act generally as a substitute for Atropine. We now know that this is only partially true, and that Homatropine, while it possesses properties of value to the oculist, acts in many respects quite differently from Atropia. Pautynski, for instance, was wrong in thinking that, since the mydriatic and cyclopegic action of Homatropine is a transient one, its irritant effects upon the uveal tract are insignificant and that it can be used to advantage where stronger mydriatics, such as Atropine, are contraindicated. Stewart* and Jackson [4] have both drawn attention to the special irritant action exerted upon the deep structures of the eye by repeated applications of a watery Solution of Hydrobromate of Homatropine, and the former thinks this is one reason why ametropia cannot be properly estimated by its use. That the employment of Homatropine Hydrobromate, when used in aqueous solution, is unequal to the task of conquering the ciliary muscle has been abundantly proved by the observations and experiments of Dabney,† Holt,[5] Oliver[6] and others, notwithstanding the experiences of Risley[7] (with Randall) and Jackson.[4] Lang and Barrett, in their classical essay, have also shown the insufficiency of the pure alkaloids even when employed in the more effective castor-oil menstruum. I have myself frequently had occasion to entertain the same doubts that Holt[5] expresses in his paper as to the value of solutions, in water, of Homatropine and its salts (however strong the solution and however frequent the instillations) for examining the usual run of cases requiring glasses. I have, for example, carefully followed Jackson's instructions, with a two per cent. aqueous solution of Merck's Homatropine instilled every ten minutes for an hour, and at the end of that time have found patients still possessing some accommodative power. Watery solutions of this, as well as of most drugs, easily flow off through the canaliculi, and for all practical purposes are lost. This will account for the necessity, which Jackson insists upon, of frequent and continued instillations if one wishes to get satisfactory results from aqueous Homatropine solutions.

More than one drop of fluid is not retained within the average sac-space. This one drop, in the case of the Homatropine Solution, acts as a stimulant to the lachrymal gland, and its secretion being added to the fluid already present, not only dilutes the latter, but also induces an overflow into the nose. From observations made upon patients during this investigation, I think I am within the truth in asserting that less than ten per cent. of aqueous solutions of Homatropine (or for that matter, of most other drugs) is retained for any effective period within the conjunctival sac.

But there is another reason why in using Homatropine there should be a *continuous* absorption of the drug. Its action upon the iris and ciliary muscle is cumulative up to a certain point and it is only by taking advantage of this cumulative property that we can hope to overcome the ciliary activity. In this important particular it differs from the fiercer action of Duboisia and Atropia, a single drop of a two per cent. solution of either alkaloid being sufficient to bring about a marked and lasting ciliary paresis. Tansley‡ has sought to prevent these unpleasant effects and this waste of material by an ingenious little

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*Philadelphia *Medical News*, March 3, 1886.

†*Medical Record*, September 15, 1888.

‡"New Instruments."—Trans. Am. Oph. Socy., 1888, p. 65.

instrument, called a canaliculus compressor. I have no doubt it is an effective expedient, but think it would not be tolerated by many patients.

The effect of Homatropine upon the accomodation is more lasting and more thorough when oleaginous menstrua and fatty excipients are employed for its application to the eye. This increased activity is, I feel convinced, entirely due to the fact that, as Green* asserts, the drug, when so exhibited, is retained within the conjunctival sac until absorption is complete. In Lang and Barrett's experiments it was found that from one drop of a two per cent. solution of the alkaloid in castor oil the fullest mydriatic and cyclopegic effects were obtained in about sixty minutes after its instillation. This thick, fatty menstruum does not pass off through the puncta, like water, but diffuses itself over the whole conjunctival and corneal surfaces until all the Homatropine with which it is charged is absorbed. Moreover, since the pure alkaloid is less soluble in albumino-saline solutions—like the lachrymal fluid—than are its salts, the former is to be preferred since the cyclopegic action is thus distributed over a longer period. All those who have used Atropia with vaseline, lanoline, etc., will appreciate the difference in effect upon the ciliary body and nasopharynx between these mixtures and watery solutions of equal strength.

That Cocaine and all its salts employed alone exert an evanescent influence upon the accommodation, is well known. As Nettleship[8] has shown (if applied persistently every few minutes for an hour) a very decided degree of cyclopegia is brought about—which begins to disappear in fifteen minutes after the last application—and the muscle regains full control in another three quarters of an hour. In conjunction with Homatropine, however, the paralyzing effects of each drug are decidedly increased. So far as I can learn we are entirely indebted to the experiments of Lang and Barrett, just referred to, for a demonstration of this truth. These observers employed a two per cent. solution, in castor oil, of the alkaloids Homatropine and Cocaine, and the results obtained are from a single application of this mixture. The following extracts from their tables will serve to illustrate the contention:

AVERAGE ACTION OF HOMATROPINE AND HOMATROPINE + COCAINE.

| | DILATATION OF PUPIL. | | RECESSION OF NEAR POINT. | RECESSION OF FAR POINT. | DIMINUTION OF RANGE OF ACC. |
|---|---|---|---|---|---|
| Time of commencement of action, in minutes . . | Hom. . . . . | 13.33 | 6.67 | . . . . | 5. |
| | Hom. + Coc. | 10. | 6.67 | . . . . | 5.83 |
| Time of maximum action, in minutes . . . . . | Hom. . . . . | 60. | 61.67 | 63.33 | 65. |
| | Hom. + Coc. | 30. | 61.67 | 77. | 59.17 |
| Time of cessation of action, in hours . . . . . | Hom. . . . . | 21.67 | 8.75 | . . . . | 8.75 |
| | Hom. + Coc. | 48. | 25.67 | . . . . | 25.67 |

*Trans. Am. Oph. Socy., 1875, p. 355.

It will thus be seen that Homatropine + Cocaine dilates the pupil and paralyzes the accommodation more rapidly than Homatropine alone, and that these results are more lasting and more decided than those following the employment of the latter.

It is a matter of speculation how Cocaine increases, as it is now known to do, the cyclopegic and iridoplegic effects of all the other mydriatics. Jourevitsch and Maklakoff* both agree that Cocaine favors the absorption of other drugs, the latter calling it the "multiplicator" of Atropine and Eserine.

Of course the greater effect of mixtures over members of a combination given singly is not a new observation in therapeutics. Witness, for example, the greater diuretic influence of the bromine and sodic salicylate compounds over the same amount of either of these agents given alone; or Brown-Sequard's discovery† that a given dose of the mixed bromides (KBr and $NH_4Br$) exerts a greater sedative influence than the same quantity of either drug. My own notion is that Cocaine renders the outer epithelial layer of the cornea (and conjunctiva) more pervious to the Homatropine or the other drug. It certainly makes it more liable to abrasion, as every one knows, and if a thoroughly cocainized cornea be carefully examined with a Coddington lens, minute fissures will often be observed running in all directions through the superfical epithelium. It is comprehensible that a similar effect is produced upon the conjunctival epithelium also, so that both miotics and mydriatics are quickly absorbed into the lymph spaces and capillaries and soon reach the interior of the eye.

Although I believe that the castor-oil mixture of Homatropine and Cocaine, introduced by Lang and Barrett, is an efficient agent in determing refractive errors, there are, it seems to me, some objections to it. In the first place an oily film forms upon the corneal surface which stands in the way of a distinct view of the fundus and even interferes somewhat with vision. I think, also, that the same film makes it more difficult, than when the oily menstruum is not employed, to decide just when the shadow "turns" in the examination by retinoscopy. These effects are partially due to the difference in the refractive indices of the cornea and castor oil and partly to the fact that the film is not always uniformily distributed over the corneal surface.

Thinking that the exhibition of *solid* Homatropine and Cocaine would best suit their peculiar cyclopegic action, I made a number of trials with these drugs, in the form of discs, with various excipients. These, used alone and in combination, were chiefly boracic acid, dextrin, linseed jelly, gum acacia, Irish moss, quince-seed jelly, marshmallow jelly, gum tragacanth, and various kinds of gelatine. These experiments led me to select discs containing a large percentage of the latter, as the best medium for exhibiting Cocaine and Homatropine, and I have had the most satisfactory results from them in single doses of one-fiftieth grain each. These discs or lamellæ were manufactured for me by Messrs. Wyeth & Brother, of Philadelphia, and in some respects are superior to the best French and English makes. They are absolutely non-irritant and immediately become soft and pliable when placed upon the ocular conjunctiva. To this they readily attach themselves and remain *in situ* until they are entirely (and *slowly*) dissolved by the lachrymal secretion. The cost

*Ann. Univ. Med. Sciences, vol. iv., 1889, p. 157.

†"The Physiological and Therapeutical Action of the Bromides."—Clark and Amory, p. 105.

of these discs is also much less than Homatropine solutions of the same strength (of which nine-tenths is probably wasted) used for determining refractive errors, because nearly all the drug is absorbed in a manner most likely to do effective work. In one disc there is exactly the same quantity of Homatropine that is contained in one minim of a two per cent. solution and I have calculated that in the lamellar form it is ten times more efficient than when dissolved in water.

The best results seem to follow the observance of these rules:

*First.*—Having dampened a small camel-hair brush, touch with it a disc previously placed on a piece of clean, dry paper, when the disc will readily stick to the brush. Telling the patient to look up, draw down the lower lid and place the opposite surface of the lamella against the exposed scleral conjunctiva, towards the outer canthus. It at once adheres to the former and the patient is now told to close the eye.

*Second.*—The patient must keep his eye shut until the examination is made. This precaution is taken to lessen the danger of an abraded cornea and to avoid the disagreeable and annoying desiccation of the corneal epithelium which sometimes follows the introduction of Cocaine into the conjunctival sac. The moisture upon the lids prevents all this.

*Third.*—The examination must begin not earlier than sixty and not later than ninety minutes after the introduction of the discs so as to take advantage of the period of maximum cycloplegia.

*Fourth.*—In persons under twenty-five, or where there is reason to suspect accommodative spasm, I supplement the single disc by another, inserted fifteen or twenty minutes after the first.

*Fifth.*—I always warn the patient that there will be a little smarting after the introduction of each disc. This, due chiefly to the Cocaine, passes off within a few minutes.

*Sixth.*—Following Lang and Barrett's experiments, I frequently introduce after the examination has been completed, a Wyeth Eserine disc (one one-thousandth grain)—made with gelatine if used shortly after the others, or a compressed disk if introduced the next day—or a single drop of the castor-oil solution (one-tenth per cent.) of Eserine. In most cases this is sufficient to make it possible for the patient to do effective work within twelve hours and in all instances within twenty-four hours. To avoid encroachment upon business time I frequently use the lamellæ in the afternoon, and, by inserting a single Eserine disc after the completion of the examination, the patient is enabled to resume near work the next morning. In cases where this is not possible I direct him to return for a second application. The great advantage of this procedure over Atropine, Duboisine and Hyoscine in the case of business men and women is apparent.

*Seventh.*—Both Cocaine and Homatropine are to some degree hygroscopic; discs prepared with these drugs should, therefore, always be kept in an air-tight receptacle.

I append short reports of a few cases, chosen from a large number, into whose eyes (after the refraction has been determined by means of discs containing one-fiftieth grain each of Cocaine and Homatropine, employed in the above mentioned manner) a one per cent. aqueous solution of Atropine had

been instilled three times daily for three days and longer. In some instances the degree of Myopia or Hypermetropia developed by the Atropine was a shade higher than from the use of the discs; sometimes it was slightly less. Occasionally there was a slight variation in the axis of the cylinder accepted by the patient. On the whole, however, the differences were not greater than those which one would expect in observations made under similar conditions by different oculists. In a number of instances the position of the near point was noted by the Landolt optometer and convex glasses at the moment of greatest cycloplegia from the discs; it did not vary from that established later on by Atropine. The refraction was measured by means of the Javal-Schiötz ophthalmometer and test lenses.

CASE I.—M. B., æt. 13. Occasional convergent squint for four or five years. Asthenopia after half-hour at school-work.

R. E. V. with + 5 D = $\frac{20}{70}$.

L. E. with sph. + 5 D ⊃ cyl. + 1 D ax. 90° = $\frac{20}{20}$.

Examined subsequently by Dr. Stevenson under Atropine with same results.

CASE II.—C. F., æt. 18. Headaches and other asthenopic symptoms.

R. E. with + 4.50 ⊃ cyl. + 1 ax. vert. = $\frac{20}{20}$ —.

L. E. with 4.50 D ⊃ cyl. + 0.75 ax. vert. = $\frac{20}{20}$.

Dr. S. reports same results from Atropine in R. E., but in L. E. + 4 D ⊃ + 1 D ax. vert. = $\frac{20}{20}$ +.

CASE III.—A. F., æt. 16, seamstress. Supraorbital headaches, etc.

L. E., + 2.50 ⊃ cyl. + 1 D., ax. 90° = $\frac{20}{50}$.

R. E., + 1.25 ⊃ cyl. + 1.25 ax. 90° = $\frac{20}{20}$—.

Atropine three days. Dr. S. reports precisely same result.

CASE IV.—Miss S. Decidedly asthenopic symptoms after reading or other near work. Dr. S. and I found the same refractive error in both eyes; I, after the use of four lamellæ in ninety minutes, and he, subsequent to four days' instillation of Atropine; *i. e.* R. and L. sph. + 3.50 ⊃ cyl. + 3.50, ax. 85° = $\frac{20}{40}$.

CASE V.—W. T., æt. 16. Has had a blepharo-conjunctivitis nearly whole life: Disc in each eye at 3 P.M.; another at 3.20. Examination at 4.15.

R. E. with —0.50 ⊃ cyl. —0.75 ax. 130° = $\frac{6}{6}$ +.

L. E. with —0.25 = $\frac{6}{6}$ +.

No change after Atropine.

CASE VI.—E. K., æt. 13. No ocular symptoms. After Discs:

R. and L. E. with + 0.50 = $\frac{6}{6}$ +.

Dr. Stevenson's report, after three days' Atropine:

"R. E. = $\frac{20}{16}$ with + 0.25. L. E., same."

I have to thank Prof. Haines, of Rush Medical College, and Dr. Stevenson, late House Surgeon of the Illinois Eye and Ear Infirmary, and Messrs. Wyeth & Brother, of Philadelphia, for their kind assistance during these investigations.

In addition to those mentioned as foot notes I am indebted for valuable information to the following instructive papers:

[1] LANG AND BARRETT: "The Action of Myotics and Mydriatics."—Oph. Hosp. Reports, vol. xi., pp. 130 and 219.

[2] SCHELL: "A New Mydriatic."—*Phila. Med. Times*, October 1880, pp. 7 and 47.

[3] PAUTYNSKI: "Pilocarpin und Homatropin."—*Klin Monätsbl. für Augenheilkunde*, 1880, S. 343.

[4] JACKSON: "Homatropine Hydrobromate."—*Phila. Med. News*, 1886, p. 88.

[5] HOLT: "The Inefficiency of Hydrobromate of Homatropine in Controlling Accommodation."—Trans. Am. Oph. Socy., 1889

[6] OLIVER: "The Comparative Action of Hydrobromate of Homatropine and of Sulphate of Atropia upon the Iris and Ciliary Muscle."—*Am. Jour. Med. Sciences*, July 1881, p. 150.

[7] RISLEY AND RANDALL: "Value of the Hydrobromate of Homatropine in Ophthalmic Practice."—Trans. Am. Oph. Socy., 1881, p. 22.

[8] NETTLESHIP: "On Cocaine in Ophthalmic Practice."—Trans. Oph. Socy., United Kingdom, vol. v., p. 226.